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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/433,777	11/03/1999	JOEL R. HAYNES	APF-18.20	2990

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EXAMINER
BECKERLEG, ANNE M

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 12/06/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/433,777	HAYNES ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *6,8-11,13,14 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,12,15-25 and 27-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response to the election/restriction requirement received on 10/02/01 has been entered. Claims 1-47 are pending in the instant application. Of these, claims 6, 8-11, 13-14, and 26 has been withdrawn as being drawn to subject matter non-elected without traverse in paper no. 7. Claims 1-5, 7, 12, 15-25, and 27-47 are elected in the instant application. An action on the merits follows.

Election/Restriction

Applicant's election without traverse of group I, claims 1-25, and 27-47 is acknowledged. In addition, applicant's election of lipids as the species of adjuvant to be examined for group I is acknowledged. The applicant, however, states that the listing of claims generic to Group I is incorrect. The applicant states that only claims 1-43 are pending in the instant application, not 1-47 as noted in the previous office action. It is noted for the record, however, that in fact 47 claims were submitted in the instant application as filed on 11/3/99. The numbering of these claims was inaccurate. On page 52 of the specification as filed, the claims after claim 26 are misnumbered as claims 23-43, which in effect creates two claims numbered 22, 23, 24, 25, and 26. The misnumbered claims were corrected under Rule 1.126 by the office. Thus, on page 52,

the claims after 26 are numbered 27, 28, 29, .. etc. In view of the correct claims numbers, the identification of generic claims by the office is correct.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27 and28 provide for the use of a composition comprising a nucleic acid molecule encoding an antigen and a non-DNA adjuvant, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 27-28 are also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 16, and 27-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The applicant claims compositions comprising a nucleic acid construct comprising a sequence encoding an antigen and an immune shift lipid adjuvant , and methods of eliciting an immune response against a selected antigen comprising delivering a nucleic acid construct comprising a sequence encoding an antigen from an infectious or parasitic disease agent and an immune shift adjuvant, wherein said lipid adjuvant shifts the immune response toward a T helper 1 or a T helper 2-type response. It is noted that the specification clearly states that the intended use of the instant compositions is for shifting the immune response in a mammal against a selected infectious or parasitic disease antigen.

The specification does not provide an enabling disclosure for shifting the immune response generated against any and all antigens, particularly infectious or parasitic disease antigens, from a Th1 to a Th2 response or vice-versa by co-administering a vector encoding an infectious or

parasitic disease antigen and any non-DNA lipid adjuvant. At the time of filing, the phenomenon of T helper cell subsets was best characterized in mice. The art recognized three T helper subsets that are defined by patterns of cytokine secretion, ability to generate cytotoxic T cells, and ability to generate particular antibody isotypes. For mice, Th1 type cells secrete primarily IL-2, IL-12, and ?-IFN and are associated with cell-mediated immunity and the production of the IgG2a antibody isotype, whereas Th2 type cells secrete primarily IL-4 and IL-5 and are associated with humoral immunity and the production of the IgG1 antibody isotype. Th0 cells secrete a mixture of cytokines and are thought to be precursors and/or intermediates of Th1 and Th2 type cells. In humans however, the heterogeneity of cytokine patterns is far more complex, with most T helper cells falling into the Th0 category.

The specification does not provide sufficient guidance for shifting the T helper immune response to an infectious or parasitic antigen using any and all vectors and promoters, any dosages or routes of administration of the vector and/or adjuvant, and any and all lipid adjuvants to any mammal. At the time of filing the prior art identifies several factors which significantly affect the generation of Th1 versus a Th2 response to an antigen which include, genetics, dose or concentration of antigen, and route of antigen administration (Abbas et al. (1996) Nature, Vol. 383, 787-793, and Golding et al. (1994) Am. J. Trop. Med. Hyg., Vol. 50 (4), 33-40). The prior art teaches that the concentration of antigen significantly affects the development of Th1 versus Th2 type responses such that low antigen concentrations preferentially induce Th1 type responses and high concentrations of antigen induce Th2 type responses (Abbas et al., supra). The

specification does not provide guidance as to the level of expression of any infectious or parasitic antigen that would result in a Th1 versus a Th2 type response or provide guidance as to the dosage of adjuvant required to shift that response from a Th1 to Th2 or vice versa. At the time of filing, many nucleic acid vectors were known in the art including adenoviral vectors, retroviral vectors, vaccinia vectors, plasmid vectors, and adeno-associated viral vectors. Further, the art recognized that viral vectors in and of themselves affect the immune response to heterologous antigens encoded therein. Typically, viral vectors generate Th1 type immune responses. The infectious and parasitic antigens themselves have also been reported to affect T helper phenotype, for example intracellular microorganisms such as Salmonella, Leishmania, Malaria and Listeria typically induce Th1 type responses, whereas schistosomiasis and Nippostongylus typically induce Th2 type responses. A further complicating factor is the genetic background of the infected mammal. The prior art contains numerous reports which demonstrate the Balb/C mice versus C57Bl/6 mice develop different T helper responses to various pathogens. The nature and route of administration of the antigen and adjuvant is also of concern to the generation of a particular T helper phenotype. Golding et al. teaches that intravenous or intraperitoneal immunization leads to preferential induction of Th1 cells whereas subcutaneous or intramuscular immunization leads to Th2 cells which may be attributable to the participation of various antigen-presenting cells (Golding et al., supra). It is further noted that the prior art of record does not teach the administration of a non-DNA adjuvant to shift the immune response to vaccination with a vector encoding a pathogenic antigen from Th1 to Th2 or vice-versa. Thus, the art at the time of filing

clearly teaches that a significant number of variables affect the generation of T helper responses, rendering the generation of a particular T helper response in any mammal unpredictable for any given pathogenic antigen.

The specification discloses that a sequence encoding an infectious or parasitic disease antigen can be administered to a mammal using any recombinant vector, any promoter, and any route of administration in combination with the administration of any "immune shift" adjuvant. The specification provides a single working example of the instant invention which demonstrates that co-administration of gold beads coated with monophosphoryl lipid A (MPL) and gold beads coated with a DNA plasmid vector encoding the carcinoembryonic antigen (CEA) under transcriptional control of the CMV promoter to the epidermis of Balb/C mice by particle-mediated bombardment compared to the administration of CEA-plasmid alone results in a decrease in the ratio of CEA specific IgG1 to IgG2a in mouse serum. It is noted that CEA is neither an infectious nor a parasitic antigen. The specification provides no data concerning the T helper cytokine patterns or level of anti-CEA cytotoxicity in the vaccinated mice. The specification suggests that this decrease in the IgG1/IgG2a ratio correlates to a shift in the T helper phenotype of the mouse's immune response to CEA from a Th2 to a Th1 type response. However, it is clear that the applicant's data does not demonstrate a "shift" from Th2 to Th1 since the overall ratio of IgG1 to IgG2a shows that the predominant isotype is IgG1 rather than IgG2a which indicates a Th2 type response. The applicant's data therefore only demonstrates a decrease in the magnitude of the Th1 type response. Thus, the skilled artisan would not find the

specification's working example evidence that the co-administration of MPL shifts the immune response generated against CEA from a Th2 type response to a Th1 type response as the mice continue to exhibit primarily IgG1 anti-CEA antibodies. Further, as discussed in the previous paragraph, the mice used in the specification's working example are Balb/C mice which have been shown to differ in the their ability to generate Th1 versus Th2 responses from other mice such as C57Bl/6. Thus, the skilled artisan would not be able to form a nexus between results obtained in Balb/C mice and the nature of T helper immune responses formed in other mice or other mammals in response to plasmid-CEA and MPL vaccination. Also, as noted above, CEA is not an infectious or parasitic disease antigen but is rather a human tumor antigen. Thus, the nature or the antigen itself is significantly different from an infectious antigen derived from a virus or bacteria, or from a parasite. Therefore, for the reasons discussed above, the skilled artisan would not consider the specification's working example as providing sufficient guidance for shifting the immune response to an infectious or parasitic antigen from Th1 to Th2 or vice versa by co-administration of any adjuvant including MPL.

Therefore, due to the art recognized complexity and unpredictability of shifting the T helper immune response to a pathogenic antigen in mammals, the breadth of the claims, and the lack of sufficient guidance from the specification concerning vector and promoter selection, level of antigen expression, genetic background of the mammal to be vaccinated, and routes of administration in regards to their affect on a) generating a particular T helper response in the absence of adjuvant and b) the ability of a particular adjuvant to shift that T helper response to

either Th1 or Th2, it would have required undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-2, 7, 12, 15, 27-29, 33, 35, 37, 39, 41, 43, and 46-47 are rejected under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No. 5,925,362, 7/29/99, filed on 8/10/94 and hereafter referred to as Spitler et al. The applicant claims compositions comprising a nucleic acid encoding an antigen and a non-DNA adjuvant and methods of eliciting an immune response using said composition. The applicant further claims said compositions and methods wherein the non-DNA adjuvant is a lipid, specifically monophosphoryl lipid A (MPL), wherein the nucleic acid is a vector, and wherein the adjuvant and nucleic acid are administered concurrently. The applicant also claims compositions comprising a nucleic acid encoding an antigen and a immune shift adjuvant and methods of eliciting or shifting an immune response using said composition.

The applicant further claims said compositions and methods wherein the adjuvant is monophosphoryl lipid A.

Spitler et al. teaches methods of eliciting immune responses in a mammal comprising the concurrent administration of a DNA expression system encoding the PSA antigen and monophosphoryl lipid A (Spitler et al., columns 7-8, and columns 9-10, claims 1-8). While Spitler et al. does not specifically teach that monophosphoryl lipid A "shifts" the immune response to PSA, case law states that "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The applicant is reminded that the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42, 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,925,362, 7/29/99, filed on 8/10/94 and hereafter referred to as Spitler et al., in view of Fynan et al. (1993) Proc. Natl. Acad. Sci. USA., Vol. 90,

11478-11482, Golding et al. (1994) Am. J. Trop. Med. Hyg., Vol. 50 (4), 33-40, and Sedegah et al. (1994) Proc. Natl. Acad. Sci. USA, Vol. 91, 9866-9870. The applicant claims compositions comprising a nucleic acid encoding an antigen and a non-DNA adjuvant and methods of eliciting an immune response using said composition. The applicant further claims said compositions and methods wherein the non-DNA adjuvant is a lipid, specifically monophosphoryl lipid A (MPL), wherein the antigen is a tumor antigen or an infectious or parasitic antigen, wherein the composition is coated on a carrier particle such as a gold bead, and wherein the composition is administered using particle mediated bombardment.

Spitler et al. teaches methods of eliciting immune responses in a mammal comprising the concurrent administration of a DNA expression system encoding the PSA antigen and monophosphoryl lipid A (Spitler et al., columns 7-8, and columns 9-10, claims 1-8). Spitler et al. differs from the instant invention by failing to teach the use biologically inert carrier particles coated with the DNA and adjuvant or particle-mediated delivery of said composition to an individual. Fynan et al. supplements Spitler et al. by teaching a method of delivering plasmid DNA to an animal for the purpose of generating an immune response by coating inert gold beads with the plasmid DNA encoding a viral antigen, Influenza hemagglutinin, and delivering them to the epidermis of the animal using a gene-gun (Fynan et al., page 11479, column 1, paragraph 5, and 11482, paragraph 2). Fynan et al. also provides motivation for delivering the composition as taught by Spitler et al. using the gene-gun technique by teaching that the amount of DNA required to elicit an immune response in a mouse using gene-gun delivery of DNA coated gold particles is

magnitudes less than that required for intramuscular injection. Thus, provided the motivation that gene-gun delivery requires far less DNA than intramuscular delivery, it would have been *prima facie* obvious to the skilled artisan to use the gene-gun technique as taught by Fynan et al. to deliver the composition as taught by Spitler et al. in order to immunize mice against an antigen with a reasonable expectation of success.

Neither Spitler et al. nor Fynan et al. teaches immunization with a malarial circumsporozoite (CS) antigen. Sedegah et al. supplements Spitler et al. and Fynan et al. by teaching the use of a plasmid encoding the malarial CS antigen to generate an anti-CS immune response (Sedegah et al., page 9866, column 2, and 9869, Figure 2). The skilled artisan would have been motivated to co-administer the monophosphoryl lipid A adjuvant with the plasmid encoding CS antigen based on the teachings of Spitler that the co-administration of the monophosphoryl lipid A adjuvant increases immune responses to antigen. Thus, based on the motivation provided by Spitler et al. for generating immune responses against an antigen by administering a DNA encoding the antigen in combination with monophosphoryl lipid A, it would have been *prima facie* obvious to the skilled artisan and the skilled artisan would have had a reasonable expectation of success at the time of filing in co-administering monophosphoryl lipid A with the plasmid encoding CS antigen taught by Sedegah et al. in order to increase the immune response to the CS antigen.

Neither Spitler, nor Fynan, nor Sedegah teaches that monophosphoryl lipid A is an "immune shift" adjuvant. Golding et al. supplements Spitler, nor Fynan, nor Sedegah by teaching

that monophosphoryl lipid A is an adjuvant that increases Th1 type immune responses against malarial antigens, particularly high titer IgG2a responses (Golding et al., page 36, column 1, paragraph 2). Thus, based on the motivation to include monophosphoryl lipid A as an adjuvant in DNA vaccination as taught by Spitler et al., and the teachings of Golding et al. that monophosphoryl lipid A increases Th1 type immune responses, it would have been *prima facie* obvious to the skilled artisan and the skilled artisan would have had a reasonable expectation of success at the time of filing in immunizing an animal with a composition comprising a plasmid encoding an antigen and an immune shift adjuvant such as monophosphoryl lipid A.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

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